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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/500,009	02/08/00	MEHTA N	P/546-221 DI

002352 HM12/0607
OSTROLENK FABER GERB & SOFFEN
1180 AVENUE OF THE AMERICAS
NEW YORK NY 10036-8403

EXAMINER	
SCHNIZER,H	
ART UNIT	**PAPER NUMBER**
1653	4

DATE MAILED: 06/07/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

FILE COPY

Office Action Summary	Application No. 09/500,009	Applicant(s) Mehta et al.
	Examiner Holly Schnizer	Group Art Unit 1653

☒ Responsive to communication(s) filed on *Feb 8, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *16-19, 21, 28-31, 39, 71, and 74* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *16-19, 21, 28-31, 39, 71, and 74* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *2*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Status of the Claims

1. The Preliminary Amendment filed April 28, 2000 has been entered. Claims 1-15, 20, 22-27, 32-38, 40-70, 72, 73, and 75-101 have been canceled. Therefore, Claims 16-19, 21, 28-31, 39, 71, and 74 are pending.

Drawings

2. The drawings filed February 8, 2000 are objected to because of the defects noted on Form PTO 948. Correction is required.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was

made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 16-19, 21, 28-31, and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koke et al. (Prot. Exp. & Purification (1991) 2: 51-58; cited in IDS) in view of Perez-Perez et al. (Biotechnology (1994) 12: 178-180; cited in IDS).

6. Koke et al. teach the construction of a vectors for high-level expression in *E. coli* of phosphatidylinositol-specific phospholipase C (PI-PLC) (page 55, column 1, line 4). The vector with the highest expression of those tested contained a coding region under the control of a lac-tac-tac triple tandem promoter (page 55, column 1, lines 6-9), as well as a STII signal codon (page 55, column 1, line 14) for targeting the expressed proteins to the periplasm, and a Shine-Dalgarno sequence (page 55, column 1, line 14). With respect to Claim 6, there is a tac promoter 5' of a second tac promoter in the 5'-lac-tac-tac-3' triple tandem promoter. These plasmids were transformed into *E. coli* host cells and evaluated for expression (page 52, column 2, line 28). Therefore, the limitations of Claims 1, 6, 7, 9, 20, 22-24, and 37 are met by the Koke et al. vectors, host cells containing the vectors, and methods of producing a protein.

7. Koke et al. do not teach that the vector contains nucleic acid coding for at least one secretion enhancing peptide.

8. Perez-Perez et al. teach that the expression of recombinant human interleukin-6 (hIL-6) as a pre-OmpA fusion in *E. coli* can be increased by supplementation with a plasmid bearing prlA4 (SecY allele) and secE genes (see abstract). Perez-Perez et al. show that addition of a plasmid

containing a polynucleotide encoding PrlA4 to a host cell expressing hIl-6 was effective in improving hIL-6 export (see p. 179, col. 1, first paragraph of Discussion). Addition of a plasmid containing a polynucleotide expressing both PrlA4 and SecE had an unexpected advantage of an accumulation of a larger amount of total hIL-6 in addition to improving pre(OmpA)-hIL-6 processing (p. 179, col. 1, second paragraph of Discussion). Perez-Perez et al. also report that overexpression of PrlA4/SecE is also effective for improving export of recombinant human granulocyte-colony stimulating factor (p. 179, col. 2, last paragraph).

9. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to add a nucleic acid sequence coding for at least prlA-4 and more preferably prlA-4 and Sec E to the plasmid as taught in Koke et al. As stated in Perez-Perez, it is well known in the art that a convenient strategy for efficient production of foreign proteins in *E. coli* is the fusion of a bacterial signal peptide as an amino-terminal leader so that the resultant fusion protein is targeted to the periplasmic space (p. 178, Col. 1, lines 1-6). It is also well known that the problem with this strategy is that the *E. coli* protein secretion machinery does not always work well (p. 178, col. 1, lines 8-9). One of ordinary skill in the art at the time of the invention would have understood this problem and would have been motivated to follow the teachings of Perez-Perez et al. to improve overexpression of proteins in bacterial cells. Placing all of the elements of Koke et al. and Perez-Perez et al. onto one plasmid would have been desirable because the plasmid could be used in the cell type of choice and it would reduce the amount of screening that would be required relative to screening for cells carrying two separate plasmids.

Therefore, it appears that the claims are unpatentable over Koke et al. in view of Perez-Perez et al.

10. Claims 71 and 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koke et al. in view of Perez-Perez et al. as applied to claims 16-19, 21, 28-31, and 39 above, and further in view of Rosenberg (Protein Analysis and Purification (1996) pp. 283-287) and Sofer et al. (Biotechniques (1983) 1(4): 198-203).

11. The teachings of Koke et al. and Perez-Perez et al. have been described above. Koke et al. and Perez-Perez et al. do not teach that the proteins (expressed using the plasmids taught therein) were recovered specifically by reverse phase followed by cation exchange chromatography or cation exchange followed by reverse phase followed by cation exchange chromatography.

12. Rosenberg teaches that cation exchange chromatography and reverse phase chromatography techniques are very well known in the art. Rosenberg states that reverse phase-HPLC separations are very rapid and reproducible (p. 300, "Reversed Phase HPLC", second paragraph). Moreover, Rosenburg states that reversed phase chromatography is a method of choice for separating small peptides (p. 300, "Reversed Phase HPLC" , second paragraph).

13. Sofer et al. teach the basic steps in optimizing a chromatography purification scheme (p. 199, Table I). Sofer et al. indicate that a systematic approach with the objective of optimizing a purification scheme, can lead to higher recoveries, enhanced yields and higher specific activities in addition to saving time and lowering costs (p. 198, col. 1, lines 14-19). Where the general

conditions of a claim (the various well known chromatography techniques) are disclosed in theprior art, it is not routine to discover the optimum ranges by routine experimentation (the combination of purification techniques that is optimal for small peptides) (see MPEP 2144.05 (IIA)). One of ordinary skill in the art would have had motivation to combine chromatography techniques as in Claims 72 and 74 in order to optimize the purification of the small peptides taught in the specification because Rosenburg teaches that reversed phase chromatography is efficient in recovering small peptides and Sofer et al. teaches that various combinations of chromatography techniques can be used in sequence to obtain optimal recovery of a protein of interest. Therefore, it appears that the claims are unpatentable over the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 306-4119. The fax phone number for Official Papers to this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Holly Schnizer, Ph.D.
June 1, 2000

Karen Cochrane Carlson PhD

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER